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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,197	10/12/2001	Olga Bandman	PF-0564 USN	3874

22428 7590 06/18/2004

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,197	BANDMAN ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *3-12,14-16 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,13,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Sequence alignments

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1, 2, 13, 17 and 18 in the reply filed on 3/31/2004 is acknowledged. The traversal is on the ground(s) that the lack of unity standard must be applied in a national stage application, and that unity of invention is accepted as between claims to polypeptide sequences and claims to the polynucleotide sequences that encode them, and that the claimed polypeptide sequences and the claimed polynucleotide sequences encoding those polypeptide sequences are corresponding technical features that are common to all of applicants' claims and that serve to technically interrelate them; and that the claimed polypeptide and polynucleotide sequences define the contribution made by each of applicants' claims over the prior art. This is not found persuasive because the claimed polynucleotides are drawn to variants having at least 90% amino acid identity to the amino acid sequence of claim 1. The claims do not recite that the sequence identity is over the entire sequence and the specification includes references to methods that would include comparison over small parts of the sequence. Thus, the claims read on polypeptides that comprise fragments of SEQ ID NO: 1 or SEQ ID NO: 2, which are polypeptides that are taught in the art as evidenced by the statements explaining the lack of unity that was set forth in the Office action mailed 3/4/2004.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-21 are pending.

Claims 3-12, 14-16 and 19-21, drawn to non-elected inventions, are withdrawn from consideration.

Claims 1, 2, 13, 17 and 18 are examined on the merits to the extent they read on sequences of SEQ ID NO: 1.

Claim Objections

3. Claim 1 is objected to as being an improper Markush claim. M.P.E.P. 803.02 states that: Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978); and *In re Haas*, 580 F.2d 461,198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, *unless the subject matter in a claim lacks unity of invention* [emphasis added], *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility. In the instant case, the products are polypeptides that are separate and structurally distinct products, which differ in structure and origin to such an extent that non-coextensive searches are required. As such, the structurally different polypeptide products have been restricted each from the other. In view of the response to the restriction requirement where applicant elected SEQ ID NO: 1, applicant is required to amend the claims to remove the reference to SEQ ID NO: 2.

Claim Rejections - 35 USC § 112

4. Claims 1, 2, 13, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because is recites improper Markush language. First the "and" is missing from the claim (should be between SEQ ID NO: 1 and SEQ ID NO: 2) and secondly, as explained above, the Markush group is improper because the two elements are separate and distinct inventions.

Claims 17 and 18 are indefinite because of the phrase "effective amount". The specification contains no teachings concerning how to determine an "effective amount" for the treatment or prevention of either a neurological disorder or a cardiovascular disorder.

5. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The disclosure does not contain an adequate written description, examples, or guidance by which variants of SEQ ID NO: 1, having at least 90% amino acid identity to the amino acid sequence of SEQ ID NO: 1, could be placed into the hands of the skilled artisan with a reasonable expectation of success without requiring undue experimentation for the following reasons.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The specification fails to define the scope of "variants of SEQ ID NO: 1 having 90% sequence identity", because the specification uses an open definition for what is meant by sequence identity so that claimed polypeptides may very little have in common with a polypeptide comprising SEQ ID NO: 1. Therefore, the variants read on polyepeptides, comprising, for example, large deletions from, or insertions or substitutions of residues within the sequence of SEQ ID NO: 1. There is a high degree of unpredictability in the protein arts so that it is very difficult to predict the effect of even small changes in amino acid sequence on protein function. Bowie et al (Science, 247: 1306-1310, 1990) teaches that while it is known that many amino acid substitutions are possible in any given protein, the position with the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Burgess et al (J. Cell Biology, 111 : 2129-2138, 1990) teaches that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar et al (Molecular and Cellular Biology, 8: 1247-1252, 1988) teaches that replacement of aspartic acid at position 47 with alanine or asparagines does not affect biological activity while replacement with serine or glutamic acid sharply reduces the biological activity of the protein. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Because of the unpredictability of the protein arts, the skilled artisan cannot make and use the broad genus of "variants" recited in the claims because such a genus encompasses an unlimited and thereby infinite plurality of amino acid substitutions, deletions, additions, or combinations thereof, as compared with the working embodiments. The disclosure does not adequately describe, provide

guidance or give examples of the critical amino acid residues that bestow upon the protein its desired characteristics.

The instant method claims encompass all types and manner of "variants", allelic variants of the exemplified polypeptided, that are not envisioned or adequately described by the disclosure. The working embodiments of the specification are a minor portion of a very broad genus and do not teach or support the majority of the genus as a whole. Furthermore, even if the genus were smaller and limited to those variants that have at least 90% sequence identity over the entire amino acid sequence of SEQ ID NO: 1, because of the unpredictability of the protein arts, one of skill in the art would not know how to use such variants because it would not be predictable that these variants possessed the same biological function.

Claim Rejections - 35 USC § 101

6. Claims 1, 2, 13, 17 and 18 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The instant application has provided a description of an isolated protein comprising the sequence of SEQ ID NO: 1. The specification refers to this product as CAREG-1. The specification asserts that it provides CAREG-1 that may be used in methods of treatment or prevention of a neurological disorder or in the treatment or prevention of a cardiovascular disorder. The specification bases the assertion that CAREG-1 may be used in the methods of treatment or prevention of a neurological disorder or in the treatment or prevention of a cardiovascular disorder on the assumption that CAREG-1 is a protein that regulates calcium ion.

CAREG-1 is assumed to regulate calcium ion because it possesses an EF-hand motif that is evidence that the protein binds calcium.

These utilities are not considered specific and substantial because the specification fails to disclose that CAREG-1 expression levels are associated with any disease or disorder. Further, the specification fails to disclose that the biological activity of CAREG-1, as a "calcium regulatory" protein has been established. While it may be true that CAREG-1 binds calcium, as does a protein having 18% sequence identity over the entire length of CAREG-1, it is not clear if this property confers upon CAREG-1 a regulatory role in calcium homeostasis. Furthermore, the specification fails to provide a definition of the term "calcium regulatory protein". Without objective evidence that CAREG-1 is associated with any disease or disorder and without evidence that the property of calcium binding confers upon CAREG-1 the ability to "regulate" calcium homeostasis, the specification merely describes a protein that has a potential role in the regulation of calcium and in neurological or cardiovascular diseases. After further research, a specific and substantial credible utility might be found for the claimed isolated proteins. This further characterization, however, is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad

interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to a protein of as yet undetermined biological significance. There is no evidence of record that would support a conclusion a CAREG-1 polypeptide of the instant application was, as of the filing date, useful for prevention and treatment of neurological and cardiovascular disorders. Until some actual and specific significance can be attributed to the protein identified in the specification as a CAREG-1 polypeptide, or the gene encoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

7. Claims 1, 2, 13, 17 and 18 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Nazarali (Nazarali, A. et al. Proc. Natl. Acad. Sci., USA, 89: 2883-2887, 1992).

Claim 2 is drawn to variants of SEQ ID NO: 1 having at least 90% sequence identity. The sequence identity is not assumed to be over the entire range of SEQ ID NO: 1.

Nazarali teaches a protein that comprises an 8 amino acid sequence in common with SEQ ID NO: 1 (see alignment; accession S20963). Therefore, Nazarali teaches a protein that has over amino acids 21-28 of SEQ ID NO: 1, at least 90% sequence identity. Therefore, Nazarali teaches a protein that is the same as that claimed.

9. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Harcourt (Accession AAR99637 of Geneseq, in AU9539013, published 30 May 1996).

Claim 2 is drawn to variants of SEQ ID NO: 1 having at least 90% sequence identity. The sequence identity is not assumed to be over the entire range of SEQ ID NO: 1.

Harcourt teaches a protein that comprises an 8 amino acid sequence in common with SEQ ID NO: 1 (see alignment; accession AAR99637 of Geneseq). Therefore, Harcourt teaches a protein that has over amino acids 76-83 of SEQ ID NO: 1, at least 90% sequence identity. Therefore, Harcourt teaches a protein that is the same as that claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
June 14, 2004

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER